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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/520,008 | 12/30/2004 | Chunyu Cao | CAO1 | 9498 |

1444 7590 11/30/2006

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| EXAMINER | |
|---|---|
| MAKAR, KIMBERLY A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | |

DATE MAILED: 11/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/520,008 | CAO ET AL. | |
| | Examiner | Art Unit | |
| | Kimberly A. Makar | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *11-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/25/06; 9/13/05; 2/04/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Response to Arguments*

1. Applicant's election with traverse of invention I in the reply filed on 09/21/06 is acknowledged. The traversal is on the ground(s) that (1) Hackett et al (US Patent 6,489,548) does not destroy lack of unity; (2) and that a search of art on invention I would be co-extensive with art for invention II. Applicants state, "that a complete search of the elected method would also require a search of the kit. Indeed, insofar as is known, the kit and the method are commonly classified, and the PTO has not alleged divergent classification sufficient to create a "serious burden" in searching and examining both groups". This is not found persuasive because Hackett et al teaches the invention as claimed (as outlined in the restriction requirements dated 08/21/06). Additionally, a search for invention I, a method for introducing a mutation into a nucleotide sequence of a target nucleic acid would not reveal art encompassing a kit comprising said method. Kits comprise more reagents, protocols, compositions than simply said method, thus requiring separate searches. Additionally, "search burden" is not a criteria for restriction under PCT (international) rules.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 11-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 09/21/06.

***Claim Rejections - 35 USC § 112***

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 recites the limitation "modified nucleotide." It is unclear from the claim as written, and the specification what the definition of "modified nucleotide" means. There is no clear definition of the phrase "modified nucleotide". The only mention of the phrase occurs on page 12 of the instant specification, where applicants state, "Alternatively, a modified nucleotide such as a modified deoxyribonucleotide, a modified ribonucleotide or an LNA (WO 99/14226) may be included in the DNA." Does this phase mean simply methylated or sulphonated nucleotides? Or a dideoxynucleotide? Does this refer strictly to a chemical modification to a single nucleotide? Or, does this encompass variegated nucleotide sequences, where multiple nucleic acids are made to encode the same protein using every known combination of codons in the sequence? Does modified mean a mutant nucleotide sequence compared to the wildtype sequence? A skilled artisan would be unable to determine the metes and bounds of the claimed invention.

***Claim Rejections - 35 USC § 102***

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-2, 4-10 are rejected under 35 U.S.C. 102(e) as being anticipated by Hackett et al (US Patent No: 6,489,458). Claims 1-2, 4-10 recites a method for introducing a mutation into a nucleotide sequence of a target nucleic acid, the method comprising the steps of preparing a DNA having an inverted repeat sequence (IR) wherein the nucleic nucleotide sequence of the DNA having an IR is homologous to a target nucleic acid and contains a mutation to be introduced into the target nucleic acid and transferring the DNA having an IR into a cell (claim 1). The method is further limited wherein the DNA having an IR has a binding motif sequence for a protein having a nuclear transport signal (claim 2). The method is further limited wherein the DNA having an IR has a modified nucleotide (claim 4). The method is further limited wherein the DNA having an IR is a double-stranded DNA (claim 5) o r a single stranded DNA (claim 6). The method is further limited wherein the target molecule is a nucleic acid located in the cytoplasm (claim 5) or in the nucleus (claim 8). The method is further limited wherein a plurality of mutations are simultaneously introduced into the target

nucleic acid (claim 9) and wherein the mutation to be introduced into the target nucleic acid is a substitution, deletion and/or insertion of a nucleotide (claim 10).

7. Hackett et al (US Patent No. 6,489,458) teaches a method of introducing mutations into a cell by using a member of the SB family of transposases (SB) and a nucleic acid fragment that includes a nucleic acid sequence with flanking inverted repeats (Column 5, lines 45-52 and Column 10, lines 55-60). The instant specification teaches that the "target nucleic acid" is "any nucleic acid" (page 7, lines 7-8) and defines mutations as "a base substitution, deletion or insertion" (page 7, lines 16-18). Specifically, Hackett teaches that the DNA to be introduced into the cells is flanked by an inverted repeat sequences (column 13, line 66 through Column 14, line 10). He teaches that the nucleotide sequence to be introduced can contain insertional, loss-of-function or gain-of-function mutations (Column 32, lines 28-33). Hackett also teaches the nucleic acid comprising IR integrates into the genome or target sequence by homologous recombination (column 14, lines 29-54). Hackett also teaches that the DNA comprising IRs comprises a binding motif for SB, a protein that has a nuclear transport signal (column 22, lines 50-57), thus allowing the DNA to bind to the SB protein, which in turn carries the DNA into the nucleus (Column 10, lines 55-60). Hackett teaches that the IRs themselves carry the sequences capable of binding to the SB protein (column 14, lines 47-53).

8. Hackett teaches that the DNA having and IR sequence can be an adenoviral vector, which is a double stranded virus (column 6, lines 4-7) or retroviral vectors, which

are single stranded viruses (column 6, lines 4-7). Hackett further teaches that the target nucleic acid is an episome (cytoplasmic) or nuclear (column 15, lines 26-32).

9. The term "modified nucleotide" is not defined in the instant specification. The brief mention of the phrase is recited on page 12 of the instant specification stating, "Alternatively, a modified nucleotide such as a modified deoxyribonucleotide, a modified ribonucleotide or an LNA (WO 99/14226) may be included in the DNA." Without a clear definition, this term reads of a broad area including variegated nucleotide sequences, where multiple nucleic acids are made to encode the same protein using every known combination of codons in the sequence. Hackett teaches that a "particular DNA sequence can be modified to employ the codons preferred for a particular cell type" (column 13, lines 33-34).

10. Furthermore, Hackett teaches his method can be used to introduce a plurality of mutations, as defined by applicant. As stated, above, applicant defines mutation as "a base substitution, deletion or insertion" (page 7, lines 16-18). Hackett teaches that his method can be used in transposon tagging (column 32, lines 4-33). In these circumstances, the DNA comprising the mutation to be introduced into the genome integrates in an endogenous chromosomal gene, rendering the chromosomal gene mutant. As such, one has now introduced two mutations: one in the IR flanked gene, and the endogenous gene that has now had an insertion rendering the gene mutant.

11. This Hackett teaches the claimed invention.

***Claim Rejections - 35 USC § 103***

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hackett el al (US Patent No: 6,489,458) in view of Dean et al (US Patent No: 6,130,207). Claim 4 recites a method for introducing a mutation into a nucleotide sequence of a target nucleic acid, the method comprising the steps of preparing a DNA having an inverted repeat sequence (IR) wherein the nucleic nucleotide sequence of the DNA having an IR is homologous to a target nucleic acid and contains a mutation to be introduced into the target nucleic acid and transferring the DNA having an IR into a cell (claim 1) wherein the DNA having an IR has a binding motif for protein with a nuclear transport signal (claim 2) wherein the protein that has the nuclear transport signal is a transcription factor (claim 4).

14. Hackett et al teaches a method for the introduction of a mutation into a target nucleic acid comprising a DNA with IR sequences that are homologous to a target sequence wherein the DNA had a binding motif for a protein having a nuclear transport signal (see above). Hackett does not teach that the DNA sequence comprises a binding motif for a transcription factor that has a nuclear localization signal.

15. Dean et al (US Patent No: 6,130,207) teaches a plasmid comprising a DNA binding sequence specific for transcription factors (Column 2, lines 54-67). Dean teaches that the binding sites allow transcription factors to bind to the plasmid and import the plasmid into the nucleus, thereby allowing the DNA to utilize the transcription factor nuclear localization signal for nuclear import (column 2, lines 54-67). Dean teaches that the binding sites can be for transcription factors such as AP1, Ap4, and Sp1 (column 3, lines 3-8). Dean teaches that the DNA to be imported into the nucleus can be flanked by IR sequences (Column 8, lines 31-50). Dean teaches the DNA insert integrates into the host genome through homologous recombination at homologous sequences (column 11, lines 2—24). Dean further teaches that two problems hinder gene therapy are, "(1) gene transfers to non-diving cells are still extremely inefficient and (2) gene transfer to specific desired non-dividing cells within a population of other cell types is even more inefficient. Thus any way to increase the amount of gene transfer will greatly benefit this emerging field" Column 1, lines 18-22) and in order to fully exploit the potential for gene therapy, there is a "continuing need for ways to increase the amount of gene transfer to cells" (column 1, lines 64-67). Dean teaches that his invention, a plasmid comprising a cell-specific nuclear targeting molecule meets this need (column 2, lines 5-27).

16. A skilled artisan at the time the invention was made would have been motivated to combine the teaching of Hackett on a method for the introduction of a mutation into a target nucleic acid comprising a DNA with IR sequences that are homologous to a target sequence wherein the DNA had a binding motif for a protein having a nuclear

transport signal with the teaching of Dean on DNA sequences for gene therapy purposes comprising IR sequences and transcription factor binding sites as a way to increase the method in which the DNA can migrate into the nucleus, not simply through the SB protein taught by Hackett, but by any transcription factor in the cell, as taught by Dean, thereby increasing the amount of gene transferred to the nucleus of the cell. IT would have been obvious to the skilled artisan to combine the teaching of Hackett on a method for the introduction of a mutation into a target nucleic acid comprising a DNA with IR sequences that are homologous to a target sequence wherein the DNA had a binding motif for a protein having a nuclear transport signal with the teaching of Dean on DNA sequences for gene therapy purposes comprising IR sequences and transcription factor binding sites as a way to increase the method in which the DNA can migrate into the nucleus, not simply through the SB protein taught by Hackett, but by any transcription factor in the cell, as taught by Dean, thereby increasing the amount of gene transferred to the nucleus of the cell – ultimately allowing for more exongenous genes to be incorporated into the host genome. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

***Conclusion***

17. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Makar, Ph.D. whose telephone number is 571-272-4139. The examiner can normally be reached on 8AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

kam/11/19/06

DAVID GUZO
PRIMARY EXAMINER